Applicants' Remarks/Arguments

I. Status

Claims 1, 3-19 and 21-36 are pending and have been examined. Applicants have amended claims 1 and 19 in order to place the claims in better form for Appeal. Specifically, the claims have been amended to explicitly reference the capability of the invention to mediate electrophoretic separations in capillary tubes that lack internal coatings. Support for this recitation may be found at page 7, lines 6-9, page 15, lines 23-27, and at page 18, line 23 – page 19, line 5. No new matter has been added by any of the requested amendments.

II. The Rejections Pursuant to 35 U.S.C. § 103

A. The Rejection of Claims 1-9, 11-13, 16-19, 21-27, 29-31 and 34-36

Claims 1-9, 11-13, 16-19, 21-27, 29-31 and 34-36 have been rejected pursuant to 35 U.S.C. § 103(a) as obvious to one of ordinary skill in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**).

Guttman *et al.* '777 is stated to disclose an aqueous gel medium (a non-cross-linked hydrophilic polymer) for facilitating the electrophoretic separation of analytes present in a sample. The Examiner has advised that the pH ranges recited in claim 1 would have been *prima facie* obvious in light of **Guttman *et al.* '777** (which is alleged to teach a pH range of 8.0-10.0, more expressly 8.0 – 8.5, and more specifically a pH of 8.3). Applicants respectfully traverse and request reconsideration.

Applicants respectfully incorporate their prior remarks concerning the express teaching of the reference to employ a pH substantially higher than the 8.0 – 8.3 pH claimed by Applicants when the anionic surfactant sodium dodecyl sulfate is employed. It is submitted that the document provides no enablement for an aqueous gel medium for

facilitating the electrophoretic separation of analytes that employs sodium dodecyl sulfate at a pH of 8.3 or less.

Applicants have amended the claims of the present application to more clearly disclose that their invention relates to an aqueous gel medium that permits electrophoretic separations of analytes (a) under alkaline conditions (b) in the presence of sodium dodecyl sulfate (c) in capillaries that do not contain internal coatings (i.e., a coating other than that provided by the separation medium itself).

As discussed in the specification and the accompanying Declaration of Dr. Lucy Liu, the ability to separate large analytes has, in the past, been impacted by several problems. Only certain polymers are capable of separating polynucleotides and proteins (page 6, lines 21-23). As analyte size increases, relative differences in charge diminish (see page 2, lines 11-20; **Guttman *et al.* '777** at column 2, lines 16 – 22). Accordingly, it is desirable to use detergents (e.g., sodium dodecyl sulfate) to denature large analytes (such as proteins and polypeptides) so that disparities in their effective charges will not distort the rate with which such molecules migrate through the electrophoretic matrix (page 2, lines 16-19; **Guttman *et al.* '777** at column 2, lines 42 - 47). Such treatment, however, entails the use of a charged medium possessing a pH greater than 3 and which thus causes the silanol groups of glass capillary tubes to ionize (see page 6, lines 29 – 30). As a consequence, aqueous gel media which contain negatively charged detergents bind only poorly to the capillary surface under such conditions (see page 6, line 21 – page 7, line 2). Such poor binding causes undesirable electroendoosmotic flow and analyte-wall interactions that distort the electrophoretic separation (see, page 4, lines 14-15).

The cited **Guttman *et al.* '777** document teaches that these problems may be addressed using capillary tubes having a permanently affixed ***coating*** on their internal surface (**Guttman *et al.* '777** at column 6, lines 44 – 51). The provided coating is stated to be formed from a bifunctional reagent having:

(A) at least one positively charged amine (for ionically binding the reagent to the negatively charged capillary surface; **Guttman *et al.* '777** at column 17, lines 8 – 13); and

(B) a functional moiety suitable for cross-linking the reagent to the gel; **Guttman *et al.* '777** at column 8, lines 8 – 10)).

As the Examiner will note, **Guttman *et al.* '777** teaches "capillary columns comprising combinations of the following: (1) a bifunctional agent which is adsorbed to the inner wall of the capillary column; (2) a gel composition copolymerized with the bifunctional agent; (3) a hydrophilic polymer adsorbed onto the polyacrylamide gel; and (4) a separation composition substantially interspersed throughout the remainder of the column" (**Guttman *et al.* '777** at column 6, lines 44 – 51). Thus, **all** of the proposed combinations comprise the recited bifunctional agent adsorbed to the inner wall of the capillary column:

(1) ***a bifunctional agent*** which is adsorbed to the inner wall of the capillary column;

(2) a gel composition copolymerized ***with the bifunctional agent***;

(3) a hydrophilic polymer adsorbed onto ***the polyacrylamide gel*** [which has been copolymerized ***with the bifunctional agent***]; and

(4) a separation composition substantially interspersed throughout the ***remainder*** of the column [i.e., that portion of the column that does not contain (1), (2), or (3); consequently some portion comprises (1), (2), or (3)].

The bifunctional reagent of **Guttman *et al.* '777** thus serves to bind the hydrophilic medium to the capillary wall, and to thereby lessen undesirable electroendoosmotic flow and analyte-wall interactions. In contrast, the present invention involves aqueous gel media that do ***not*** bind to the capillary wall (see page 12, line 26), but which nevertheless achieve desirable molecular size separations. As discussed on page 12, line 26 – page 13, line 7, such an achievement was unexpected. The invention is

thus predicated, in part, upon the recognition that by dissolving hydrophilic polymers into a high concentration tris-borate buffer a separation medium is produced which suppresses electroosmotic flow and reduces analyte-surface interactions, and which therefore can be used in ***uncoated*** capillary tubes in capillary electrophoresis to provide a molecular sieve. In this regard, the Examiner's attention is respectfully directed to **Figure 2** (lower two curves) of the Application which shows the poor resolution of capillary electrophoresis when conducted using hydrophilic polymers and uncoated capillary tubes. In contrast, the upper curve of **Figure 2** shows the capability of the aqueous medium of the present invention to act as a molecular sieve in capillary electrophoresis with ***uncoated*** capillary tubes.

It is respectfully submitted that **Guttman *et al.* '777** does not teach or suggest, or predict, an aqueous gel medium which facilitates the electrophoretic separation of analytes via capillary electrophoresis using an ***uncoated*** capillary tube, nor a capillary electrophoresis system comprising an ***uncoated*** capillary tube. Accordingly, Applicants submit that **Guttman *et al.* '777** does not render the presently claimed invention obvious.

Applicants additionally submit that those of ordinary skill would not have concluded that **Guttman *et al.* '777** taught the inclusion of reagent(s) that function to help keep protein analytes in a reduced form ***in*** the aqueous gel medium as is claimed by Applicants. The Examiner has advised that **Guttman *et al.* '777** does disclose the inclusion of reducing reagents such as dithiothreitol and 2-mercaptoethanol with the sample, and has suggested that such reducing reagents, by virtue of their small size, would diffuse into the gel material and thus serve to keep analytes in a reduced form. Applicants respectfully request reconsideration of this conclusion.

It is submitted that those of ordinary skill would have concluded that **Guttman *et al.* '777** teaches the use of a reducing reagent solely for the purpose of sample preparation; i.e., "***before*** introduction into the capillary column" (see column 18, lines 41-42, emphasis added). It is therefore respectfully submitted that the Examiner's conclusion fails to appreciate two consequences of such use. First, the conclusion fails to

address the fact that analyte molecules, by virtue of their size and charge will migrate in capillary electrophoresis and thus will separate away from the uncharged reducing reagents. Accordingly, such reducing reagents, even if provided by **Guttman *et al.*** '777, would be incapable of functioning to help ***keep*** protein analytes in a reduced form, as is presently claimed, since the protein analytes and the reducing reagents would be continuously migrating further and further apart. As the Examiner will appreciate, even if charged reducing reagents were employed, such molecules would migrate faster than the larger protein analytes and would thus also separate from such analytes. Second, any capability of such reducing reagents to help ***keep*** protein analytes in a reduced form in the method of **Guttman *et al.*** '777 would of course be dependent on their presence at a concentration sufficient to mediate such function. In light of the active and/or differential mobility of the analytes, it is respectfully submitted that the method of **Guttman *et al.*** '777 would provide no means for ***maintaining*** the concentration of such reducing reagents at a level sufficient to ***keep*** protein analytes in a reduced form.

In contrast, including such reagents within the aqueous gel media (as presently claimed) causes them to be present at substantially the same concentration throughout the entire region of the gel. As a consequence, analytes are not migrating away from the reducing reagents and the concentration of the reducing reagents may be maintained at a level sufficient to permit the reducing reagents to function to help ***keep*** protein analytes in a reduced form.

Applicants therefore submit that those of ordinary skill would not have found it obvious in light of **Guttman *et al.*** '777 to have included reducing reagent(s) that function to help ***keep*** protein analytes in a reduced form ***within*** the employed aqueous gel medium.

In light of Applicants' amendments and the above remarks, Applicants respectfully submit that the rejection of claims 1-9, 11-13, 16-19, 21-27, 29-31 and 34-36 pursuant to 35 U.S.C. § 103(a) in light of U.S. Patent No. 5,370,777 (**Guttman *et al.*** '777) may now be properly withdrawn.

B. The Rejection of Claims 10 and 28

Claims 10 and 28 have been rejected pursuant to 35 U.S.C. § 103(a) as obvious to one of ordinary skill in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**) in view of U.S. Patent No. 3,622,661 (**King *et al.***). **King *et al.*** is cited as evidence that commercially available dextran possesses a non-cross-linked structure composed of approximately 95% alpha-D-(1-6) linkages, and that the use of such compositions is "conventional" in toothpastes (the reference providing no teaching or suggestion, or prediction, related to the use of any compositions in capillary electrophoresis). Applicants respectfully traverse and request reconsideration.

Applicants note that although **King *et al.*** discloses the nature and percentage of the dextran linkages, it does not appear to teach, suggest or predict the use of dextran compositions having the molecular weight recited in applicants' claims. **Guttman *et al.* '777** does not remedy this deficiency, since it provides no basis for concluding either the inherency of dextran molecular weights or that the dextran employed by **Guttman *et al.* '777** meets the nature and percentage of the dextran linkages recited in the claims.

It is submitted that the combined teachings or suggestions of, or predictions based upon, the reference thus fail to render the claimed invention obvious. Applicants respectfully submit that claims 10 and 28 comprise the recitations of amended claims 1 and 19, and accordingly are patentable for the reasons stated with respect to such claims the rejections based on **Guttman *et al.* '777**. It is submitted that **King *et al.*** fails to teach or suggest, or predict: (A) the use of uncoated capillary tubes and (B) the use of an aqueous gel medium capable of facilitating the electrophoretic separation of analytes via capillary electrophoresis using an uncoated capillary tube by comprising a molecular sieve, as presently claimed. Thus, the combined teachings or suggestions of, or predictions based upon, the references fail to render the present invention obvious.

In light of Applicants' amendments and the above remarks, Applicants respectfully submit that the rejection of claims 10 and 28 pursuant to 35 U.S.C. § 103(a)

in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**) as combined with U.S. Patent No. 3,622,661 (**King *et al.***) may now be properly withdrawn.

C. The Rejection of Claims 14-15 and 32-33

Claims 14-15 and 32-33 have been rejected pursuant to 35 U.S.C. § 103(a) as obvious to one of ordinary skill in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**) in view of U.S. Patent No. 5,213,669 (**Guttman '669**). **Guttman '669** is stated to teach an aqueous gel medium having an alcohol that is glycerol. Applicants respectfully traverse and request reconsideration.

Applicants submit that claims 14-15 and 32-33 comprise the recitations of claims 1 and 19, and accordingly are patentable for the reasons stated with respect to such claims the rejections based on **Guttman *et al.* '777**. It is submitted that **Guttman '669** fails to teach or suggest, or predict, the use of a tris borate buffer in an aqueous gel medium, and **Guttman *et al.* '777** fails to teach or suggest, or predict, the use of uncoated capillary tubes or media for use in uncoated capillary tubes. Accordingly, it is submitted that the combined teachings of these documents would not have taught, suggested, or predicted the use of a tris borate buffer in an aqueous gel medium for use in an uncoated capillary tube.

Additionally, Applicants note that the compositions recited within the presently claimed inventions provide unexpectedly better results than those obtainable using the compositions of **Guttman '669** (please see Example 5 of the present application).

In light of Applicants' amendments and the above remarks, Applicants respectfully submit that the rejection of claims 4-15 and 32-33 pursuant to 35 U.S.C. § 103(a) in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**) as combined with U.S. Patent No. 5,213,669 (**Guttman '669**) may now be properly withdrawn.

III. Concluding Remarks

Applicants submit that the present response is complete and complies with the requirements of 35 U.S.C. §121. The Application is believed to be in condition for Allowance and early notice of such favorable action is respectfully requested. Should the Examiner have any remaining questions regarding the subject invention or its patentability, Applicants encourage the Examiner to contact the undersigned to answer such questions or provide any desired additional information.

Respectfully Submitted,

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